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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	)	Before the Examiner
Stefano Carlino	)	Elli Peselev
	)	
Serial No. 10/523,657	)	Group Art Unit: 1623
	)	
Filing Date: February 4, 2005	)	Attorney Docket: LABM-10
	)	
PROCESS FOR PREPARING A STERILE HIGH MOLECULAR WEIGHT HYALURONIC ACID FORMULATION	)	April 14, 2009

AMENDED APPEAL BRIEF (37 C.F.R. §41.37)

Mail Stop Appeal Briefs-Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amended Appeal Brief is in reply to the Notification of Non-Complaint Appeal Brief mailed April 8, 2009. Applicant's Appeal Brief now fully complies with new rule 36 C.F.R. §41.37. No extensions of time are believed to be necessary, but if any are deemed to be due, please charge the fees therefore to Deposit Account 12-2424.

I hereby certify that, on the date shown below, this correspondence is being deposited with the United States Postal Service in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 as "Express Mail Post Office to Addressee."

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Printed Name of Person Mailing

April 14, 2009
Date

I. REAL PARTY IN INTEREST
(37 C.F.R. §41.37(e)(1))

The real party in interest in this appeal is the Assignee, Laboratoire Medidom S.A.

II. RELATED CASES
(34 C.F.R. §41.37(e)(2))

With respect to other cases that are related to, or will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal; there are none.

III. JURISDICTIONAL STATEMENT
(34 C.F.R. §41.37(e)(3))

The statute under which this appeal is taken is 35 U.S.C. §134(a) (Appeal to the Board of Patent Appeals and Interferences).

The final Office Action setting out the rejection on appeal was issued on September 25, 2008.

The Notice of Appeal, together with a petition for extension of time of one (1) month under 37 C.F.R. §1.136(a) (PTO/SB/22), was filed on January 15, 2009.

The Appeal Brief is being filed on February 18, 2009.

IV. TABLE OF CONTENTS
(37 C.F.R. §41.37(e)(4))

V. TABLE OF AUTHORITIES
(37 C.F.R. §41.37(e)(5))

There are none cited.

VI. STATUS OF AMENDMENTS
(37 C.F.R. §41.37(e)(7))

No amendments were filed after the final rejection.

VII. GROUNDS OF REJECTION TO BE REVIEWED
(37 C.F.R. §41.37(e)(8))

Claims 1 and 4-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7 and 8 of U.S. Patent No. 6,489,467.

Claims 1 and 4-9 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 00/44925 in view of EP 0631799 A1.

VIII. STATEMENT OF FACTS
(37 C.F.R. §41.37(e)(9))

The present invention is directed to a process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt at a specified concentration [p 2 [0026]], comprising the steps of providing an aqueous formulation comprising high molecular weight hyaluronic acid salt at a concentration of less than the specified concentration[p 2 [0027]; Figure 1, step 4]; passing the aqueous formulation through a filter having a pore size of less than 0.45 μm [p 2 [0028]; p 3 [0050]] and greater than 0.1 μm [p 3 [0050]; Figure 1,

step 7]; concentrating the aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached [p 2 [0029]]; wherein from the concentration step the pharmaceutical formulation is filled directly into sterile recipients ready for pharmaceutical use [p 2 [0030]], or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use [p 4 [0058]; Figure 1, steps 14-16; original claim 4].

Previously used methods for the preparation of ready-to-use pharmaceutical formulations of hyaluronic acid involve measuring out a defined precise quantity by weight of hyaluronic acid, which is then mixed with a precise volume of water and precise quantities of excipients [p 1 [0016]]. The formulation is then filled into syringes and vials, and subsequently sterilized by autoclave, with the associated problems of degradation of hyaluronic acid molecular chains on heat sterilization [p 1 [0016]]. Even where the preparation of the ready-to-use aqueous formulation of hyaluronic acid salt is carried out starting from a pre-sterilized powder of hyaluronic acid salt [p 1 [0020]], this powder must be measured in an accurate amount and added to a precise quantity of water, and precise amounts of excipients [p 1 [0016]], in order to get the required accurate concentration of the pharmaceutical formulation necessary for medical applications [p 2 [0033]]. The measuring and mixing of the sterilized powder necessarily requires removal of the sterilized powder from the storage vessel transfer to a measuring vessel, and to the vessel in which it will be

mixed with water. Not only is this process cumbersome, but also in all of the steps there is introduced a risk of contamination of the sterile powder [p 1 [0031]].

An alternative process for preparing ready-to-use hyaluronic acid pharmaceutical formulations is reported in US 5,093,487 (cited in the present application) [p 2 [0023]], which involves filtering a concentrated solution of hyaluronic acid aqueous formulation by means of multiple passes through a 0.2 μm filter, so as to irreversibly reduce the viscosity of the hyaluronic acid [p 2 [0023]]. The process of US 5,093,487 not only causes an irreversible reduction of the viscosity, but also it is not possible to control the homogeneous viscosity of the hyaluronic acid salt solution after such multiple filtration steps, such that viscosity variations may occur from one batch of hyaluronic acid formulation to another [p 2 [0022] [0023]]. This irreversible reduction of the viscosity of the hyaluronic acid, and the variability of viscosity of batches of sterilised formulation, are undesirable for pharmaceutical applications of hyaluronic acid such as intra-articular and ocular applications [p 2 [0023]].

Whereas, in contrast to the previously taught methods for preparing ready-to-use pharmaceutical formulations of hyaluronic acid, the process of the present invention as claimed allows for the preparation of sterile pharmaceutical formulations of high molecular weight hyaluronic acid salt directly ready for pharmaceutical use, in which the required properties of high molecular weight of

hyaluronic acid and determined high viscosity are maintained [p 2 [0030], [0032], [0033]]. No additional preparation or sterilisation steps are required before pharmaceutical use of the hyaluronic acid salt formulations prepared to the present invention [p 1 [0017], [0022]; p 2 [0030], [0035]]. The process of the present invention avoids the need for additional manipulations of weighing out accurately specific amounts of sterilized concentrated sodium hyaluronic powder [p 1 [0016]], mixing the powder with a defined precise volume of water and precise quantities of excipients, since the concentration of the formulation is accurately monitored to arrive at the desired specified concentration during the vacuum concentration step [p 2 [0033]]; and avoids the associated risks of contamination due to the removal of the sterilized hyaluronic acid salt powder from a storage vessel, transfer to a measuring vessel and then transfer to a vessel in which the powder would be mixed with water, before finally being filled into recipients for pharmaceutical use, encountered in the preparation of pharmaceutical formulations by the conventional methods [p 1 [0016], [0017], [0020], [0022], [0023]]. In order to meet health authority standards for administration in the human body, the aqueous formulations prepared from sterilized hyaluronic acid salt powder by prior art conventional methods must be subjected to further sterilization, such as by autoclaving of the formulation filled in vials or syringes before it may be used for pharmaceutical use [p 1 [0016]]. This is

not necessary for the sterile ready for pharmaceutical use formulations of high molecular weight hyaluronic acid salt of the present invention [p 2 [0030]].

IX. ARGUMENT
(37 C.F.R. §41.37(e)(10))

Turning specifically to the Examiner's rejection of the pending claims on the ground of a non-statutory obviousness type double patenting over US patent No. 6,489,467, please consider the following.

The invention claimed is not the use of evaporation under vacuum to concentrate a solution comprising hyaluronic acid [p 7, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007], but on the contrary lies in the provision of a process for preparing a sterile, ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt at a specified concentration [p 4, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007], involving the specific combination of the steps of; providing an aqueous formulation comprising high molecular weight hyaluronic acid salt at a concentration of less than the specified concentration; passing said aqueous formulation through a filter having a pore size of less than 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached [p 4, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007]; and after the concentration step filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently

directly into sterile recipients ready for pharmaceutical use [p 5, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 4 and 7-8, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007].

Contrary to the presently claimed invention, US 6,489,467 claims a process for purifying hyaluronic acid salt powder, which process involves the steps of diafiltration (step a) and the removing of cells (step b) from an aqueous solution of hyaluronic acid obtained from a biological source, followed by subsequently sterilizing the thus purified hyaluronic acid salt containing solution (step c) [p 2, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. In the method of US 6,489,467 the sterilization step is carried out by passing the purified hyaluronic acid salt containing solution through a 0.2 μm filter (col.6 lines 9-23, col.7 lines 51-54, col.8 lines 63-67, claims 8, 19, 27) [p 2, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. According to US 6,489,467, the thus obtained solution may then be freeze dried to obtain a dry powder of purified hyaluronic acid salt [p 2, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. It is described in US 6,489,467 (see col. 6 lines 27-32) that after the sterilization step the solution may be pre-concentrated by filtration through a filter of pore size 5'000 – 10'000 Daltons nominal molecular weight cut off before freeze drying to obtain a dry powder of

hyaluronic acid salt [p 2-3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. This concentration by filtration is carried out solely to permit the subsequent freeze drying of the hyaluronic acid salt to obtain a dry HA powder [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. Concentration by filtration as taught by US 6,489,467 produces a wet hyaluronic acid salt containing residue suitable for freeze drying to obtain the purified hyaluronic acid salt dried powder [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The concentration by filtration described in US 6,489,467 is not intended for and cannot be used for providing a concentrated aqueous solution of hyaluronic acid salt at a specified concentration of hyaluronic acid salt [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

US 6,489,467 does not disclose, or make obvious in any way the process for preparing a sterile, ready-to-use aqueous pharmaceutical formulation of hyaluronic acid salt at a specified concentration involving the specific combination of steps of providing an aqueous formulation comprising high molecular weight hyaluronic acid salt at a concentration of less than the specified concentration; passing said aqueous formulation through a filter having a pore size of less than 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and wherein after the

concentration step, the pharmaceutical formulation is filled directly into sterile recipients ready for pharmaceutical use [p 4, 6 and 7-8, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

It may further be highlighted that US 6,489,467 teaches a method of preparing purified hyaluronic acid, in the form of a dry powder, which can then be used for the preparation of pharmaceutical compositions in a conventional manner (reference may be made to, for example, col. 7 lines 55-57 and col. 8 lines 3-5) [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The skilled person reading US 6,489,467 is, accordingly, taught a method for arriving at pharmaceutical formulations of hyaluronic acid salt, starting from dry purified hyaluronic acid salt powder, by conventional methods [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The skilled person on reading US 6,489,467 has, accordingly, a method for arriving at pharmaceutical formulations of hyaluronic acid salt by conventional methods and has no reason whatsoever to look for any other method for preparing pharmaceutical formulation of hyaluronic acid salt [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. On the basis of the teaching of US 6,489,467 it is totally unobvious for the skilled person to decide to stop following the method of US 6,489,467 after the step of sterilization by filtration, and then to

instead subject this sterilized solution to a step of concentration under vacuum to a specific accurate pharmaceutical concentration, followed by filling directly into sterile recipients with the aim to provide an aqueous pharmaceutical formulation of high molecular weight hyaluronic acid salt ready for pharmaceutical use as required by the present invention as claimed [p 3-4, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. It is clear that the Examiner's objection is entirely based on unallowable hind-sight reasoning [p 4 Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Turning to the Examiner's rejection of the pending claims on grounds of obviousness under 35 U.S.C. 103 (a) over WO 00/44925 in view of EP 0 631 799 A1, please consider the following.

WO 00/44925 is the International Application (No. PCT/IB00/00082) from which the cited patent US 6,489,467 is derived, and the description and examples of US 6,489,467 are identical with those of WO 00/44925.

Accordingly, WO 00/44925 is directed to a process for purifying high molecular weight hyaluronic acid, involving steps of diafiltration and removing of cells from an aqueous solution of hyaluronic acid obtained from a biological source, followed by sterilizing the obtained hyaluronic acid salt containing solution by passing a 0.2 μm filter [p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 4, Applicant's reply mailed on June 9, 2008 to

Office Action mailed January 9, 2008]. WO 00/44925 teaches that the filter sterilized hyaluronic acid salt containing aqueous solution may optionally be freeze dried to obtain a dry powder of hyaluronic acid salt in purified form (see, for example, page 10 last 5 lines of WO 00/44925 as published) [p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 4, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The process taught by WO 00/44925 produces a sterilised purified dry powder of hyaluronic acid salt [p 4, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007] and not an aqueous sterile pharmaceutical formulation of hyaluronic acid salt ready for pharmaceutical use [p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007]. Indeed, WO 00/44925 teaches that the freeze dried dry powder of hyaluronic acid salt may subsequently "be used for preparing pharmaceutical compositions" (see for example page 13 paragraph 6 to page 14 first full paragraph, page 15 last two paragraphs to end of page 16) [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007].

Before the concentrated hyaluronic acid salt powder product of the process of WO 00/44925 can be used for pharmaceutical applications it must be prepared into a ready-to-use pharmaceutical formulation in the conventional manner, as

discussed above [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007]. That is to say by weighing out accurately a specific amount of the sterilised concentrated sodium hyaluronate powder, mixing this powder with a defined precise volume of water and precise quantities of excipients, in order to get the required accurate concentration of hyaluronic acid salt in the aqueous formulation necessary for pharmaceutical use [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5-6, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007], with the associated risks of contamination due to the removal of the sterilized hyaluronic acid salt powder from a storage vessel, transfer to a measuring vessel and then transfer to a vessel in which the powder would be mixed with water, before finally being filled into recipients for pharmaceutical use [p 4-5, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007]. In order to meet health authority standards for administration in the human body the thus prepared aqueous formulation must be subjected to further sterilisation, such as by autoclaving of the solution filled in vials or syringes [p 6, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007].

WO 00/44925 does not teach or even suggest in any way a step of concentrating a sterile aqueous solution of hyaluronic acid salt to a specific accurate pharmaceutical concentration [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007]. Nor is there taught or even suggested any step of filling such a sterilised aqueous pharmaceutical formulation of hyaluronic acid salt, at a specific accurate pharmaceutical concentration, directly into sterile recipients ready for pharmaceutical use [p 5, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. Indeed, the filtered solution obtained by step (c) of the process of WO 00/44925 is not a pharmaceutical formulation "ready for pharmaceutical use" as required by the claims of the present application [p 5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The aqueous solution containing high molecular weight hyaluronic acid salt, obtained after steps (a) and (b), subjected to the described step of sterilization by filtration through a filter having a 0.2 μm pore size has necessarily a low concentration of hyaluronic acid not suitable for pharmaceutical application [p 5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. At the concentrations of 1 to 3% hyaluronic acid salt required for high viscosity aqueous hyaluronic acid salt formulations for pharmaceutical use, not all of

the hyaluronic acid salt would pass through a filter of 0.2μm pore size as taught for the sterilization step in WO 00/44925 [p 5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. This results in significant reduction in the concentration of hyaluronic acid salt and/or irreversible degradation of the high molecular weight hyaluronic acid salt, i.e. reduction of molecular weight of hyaluronic acid salt and reduction of viscosity, not acceptable for pharmaceutical applications (as described in the present application as filed page 4 last paragraph to page 5 first paragraph) [p 5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

According to WO 00/44925 the sterilized hyaluronic acid salt containing solution is freeze-dried to obtain a dry hyaluronic acid salt powder [p 5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. WO 00/44925 teaches that the dry hyaluronic acid salt purified powder may subsequently be used for preparing pharmaceutical compositions [p 5, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

In other words, WO 00/44925 provides the skilled person with a method for purifying high molecular weight hyaluronic acid from a biological source and for preparing pharmaceutical formulations of this purified hyaluronic acid salt by conventional methods starting from the freeze-dried purified hyaluronic acid salt

powder, i.e. by weighing out an accurate quantity of the dry hyaluronic acid salt powder and dissolving this in an accurate volume of water, with the addition of accurately measured quantities of desired excipients to provide an aqueous pharmaceutical formulation [p 5, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The skilled person reading WO 00/44925 is thus taught how to go about preparing a pharmaceutical formulation of hyaluronic acid salt and none of the cited prior art documents provide the skilled person with any reason to look for an alternative method for preparing sterile aqueous formulation of high molecular weight hyaluronic acid salt ready for pharmaceutical use [p 5-6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5-6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. Since the skilled person is taught by WO 00/44925 to prepare pharmaceutical formulations from the freeze-dried powder of hyaluronic acid salt, it is totally unobvious from the teaching of the cited prior art for the skilled person to instead stop at the step (c) of sterilization of the purified hyaluronic acid salt of WO 00/44925 and, instead of following the teaching of WO 00/44925, on the contrary to concentrate the aqueous solution by applying a vacuum and boiling off water until a pre-specified accurate pharmaceutical concentration is reached [p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]; and then filling the formulation directly into sterile recipients, as required by present

invention as claimed [p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

The Examiner cites EP 0 631 799, which is directed to a vacuum concentrating plant in which a feed liquid is heated indirectly by a latent heat produced by introducing depressurized vapour into a steam jacket, with the aim of providing high heat efficiency [p 7, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. There is nothing whatsoever in EP 0 631 799 that provides any motivation whatsoever to a skilled person to introduce the vacuum concentration process described therein into the purification process described in WO 00/44925 at any step in the process described therein, i.e. after any of the steps (a), (b), or (c), let alone to suggest to the skilled person any reason for wishing to apply the vacuum concentration method of EP 0 631 799 specifically to the sterilized solution produced after the filter sterilization step (c) of WO 00/44925 [p 7, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Furthermore, even if the person skilled in the art were inventively to desire to apply the vacuum concentration process of EP 0 631 799 to the sterilized hyaluronic

acid salt containing solution produced in step (c) of the process of WO 00/44925, he would not arrive at the present invention as claimed [p 7, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. EP 0 631 799 does not provide any teaching of the preparation of pharmaceutical formulations having an accurate, pre-determined concentration claimed [p 7, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 7, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. Indeed, EP 0 631 799 does not describe or suggest how any means for monitoring of the concentration of the liquid in the vacuum evaporator during the concentration process, or means for stopping the vacuum evaporation concentration process in the apparatus described therein abruptly when the desired concentration of substrate has been reached [p 7, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007], could be integrated into the apparatus described in EP 0 631 799, or even whether it would be feasible to do so [p 7, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. Further, EP 0 631 799 does not provide any teaching whatsoever of the filling of a pharmaceutical formulation, having a specified pharmaceutical concentration of HA directly into sterile recipients ready for pharmaceutical use [p 7, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 7, Applicant's reply mailed on December 6, 2007 to

Office Action mailed September 7, 2007; p 7, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Finally, with respect to claim 8 of the present application on file, it is respectively submitted that WO 00/44925 does not disclose the measurement of hyaluronic acid salt concentration with a spectrophotometer sensing wave radiation absorption in the formulation as required by claim 8 of the present application [p 8, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. To the contrary, WO 00/44925 describes in step (a) of the purifying process that the visco-elastic aqueous solution/broth containing the high molecular weight hyaluronic acid is preferably diafiltered until the "filtrate which is disgarded as an optical density at a wave length of 280 nm equal or lower than 0.02" (page 7 last paragraph to page 8 first paragraph) [p 8, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. What is described in WO 00/44925 is that the acidified hyaluronic acid salt containing broth from biological source is diafiltered on a filter having a pore size in the range 100'000 Daltons to 0.45 μm, whereby at the acidic pH of pH 1.7 to 3.3 a cross-linked network of hyaluronic acid salt molecules is formed that is retained on the filter, whereas proteins and other material impurities pass through the filter (i.e. separating the HA from soluble impurities contained in the solution) (see for example page 6 of WO 00/44925) [p 8, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Accordingly, in the cited passage at page 7 last paragraph to page 8 first paragraph, what is described is the measuring of the optical density of the filtrate of this diafiltration, after each diafiltration to measure the level of impurity in the filtrate, in order to determine when sufficient repeats of the diafiltration purification step have been effected [p 8, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. There is no teaching whatsoever of the use of a spectrophotometer sensing wave radiation absorption to monitor hyaluronic acid salt concentration in-situ in a step of concentration of a solution of hyaluronic acid salt to a pre-determined specified concentration as required by claim 8 [p 9, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Respectfully submitted,

Date: April 14, 2009

By: _____

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KD_IM-1933187_1.DOC

APPENDIX

CLAIM SECTION

(37 C.F.R. §41.37(e)(11))

1. (Rejected) A process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration, comprising the steps of:

- providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration;

- passing said aqueous formulation through a filter having a pore size less than 0.45 μm; and greater than 0.1 μm;

- concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and

- after the concentration step, filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use.

2. (Cancelled)

3. (Cancelled)

4. (Rejected) Process according to claim 1, wherein the vacuum is at a pressure in the range of 30 to 60 millibars.

5. (Rejected) Process according to claim 1, wherein the average molecular weight of HA is in the range of 800'000 to 5'000'000 Daltons.

6. (Rejected) Process according to claim 1, wherein the filter has a pore size in the range of 0.22 μm to 0.1 μm.

7. (Rejected) Process according to claim 1, wherein, during the concentration step, the concentration of HA is measured in real time and the vacuum boiling process is stopped automatically when the specified concentration is measured.

8. (Rejected) Process according to claim 1, wherein the HA concentration is measured with a spectrophotometer sensing wave radiation absorption in the formulation.

9. (Rejected) Process according to claim 1, wherein excipients are added to the formulation after the filtration step, and wherein the conductivity of the HA formulation is measured in real time until the amount of excipients reaches a required value.

APPENDIX

CLAIM SUPPORT AND DRAWING ANALYSIS SECTION
(37 C.F.R. §41.37(e)(11))

1. (Rejected) A process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration, comprising the steps of :

- providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration;

- passing said aqueous formulation through a filter having a pore size less than 0.45 μm; and greater than 0.1 μm **{p 3 [0050], lines 4-8}**;

- concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and

- after the concentration step, filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use **{p 2 [0030], lines 6-10; p 4 [0058], lines 1-7; original claim 2}**.

2. (Cancelled)

3. (Cancelled)

4. (Rejected) Process according to claim 1, wherein the vacuum is at a pressure in the range of 30 to 60 millibars.

5. (Rejected) Process according to claim 1, wherein the average molecular weight of HA is in the range of 800'000 to 5'000'000 Daltons.

6. (Rejected) Process according to claim 1, wherein the filter has a pore size in the range of 0.22 μm to 0.1 μm **{p 3 [0050], lines 4-8; original claim 6}**.

7. (Rejected) Process according to claim 1, wherein, during the concentration step, the concentration of HA is measured in real time and the vacuum boiling process is stopped automatically when the specified concentration is measured.

8. (Rejected) Process according to claim 1, wherein the HA concentration is measured with a spectrophotometer sensing wave radiation absorption in the formulation.

9. (Rejected) Process according to claim 1, wherein excipients are added to the formulation after the filtration step, and wherein the conductivity of the HA formulation is measured in real time until the amount of excipients reaches a required value.

APPENDIX

MEANS OR STEP PLUS FUNCTION ANALYSIS SECTION
(37 C.F.R. §41.37(e)(11))

There are none.

APPENDIX

EVIDENCE SECTION
(37 C.F.R. §41.37(e)(11))

There is none.

APPENDIX

RELATED CASES SECTION
(37 C.F.R. §41.37(e)(11))

There are none.

LABM-10
CWB

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10/523,657 ✓	02/04/2005	Stefano Carlino	LABM-10 ✓	9578

52450 7590 04/08/2009

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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 04/08/2009

Please find below and/or attached an Office communication concerning this application or proceeding.

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DUE: 5-8-2009 *
10-8-2009

Notification of Non-Compliant Appeal Brief (37 CFR 41.37)	Application No.	Applicant(s)	
	10/523,657	CARLINO, STEFANO	
	Examiner	Art Unit	
	ELLI PESELEV	1623	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *18 February 2009* is defective for failure to comply with one or more provisions of 37 CFR 41.37.

To avoid dismissal of the appeal, applicant must file anamended brief or other appropriate correction (see MPEP 1205.03) within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☒ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☒ The brief does not contain a statement of the status of all claims, (e.g., rejected, allowed, withdrawn, objected to, canceled), or does not identify the appealed claims (37 CFR 41.37(c)(1)(iii)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 41.37(c)(1)(iv)).

4. ☒ (a) The brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters; and/or (b) the brief fails to: (1) identify, for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function under 35 U.S.C. 112, sixth paragraph, and/or (2) set forth the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification by page and line number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(v)).

5. ☐ The brief does not contain a concise statement of each ground of rejection presented for review (37 CFR 41.37(c)(1)(vi))

6. ☐ The brief does not present an argument under a separate heading for each ground of rejection on appeal (37 CFR 41.37(c)(1)(vii)).

7. ☒ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(viii)).

8. ☒ The brief does not contain copies of the evidence submitted under 37 CFR 1.130, 1.131, or 1.132 or of any other evidence entered by the examiner **and relied upon by appellant in the appeal**, along with a statement setting forth where in the record that evidence was entered by the examiner, as an appendix thereto (37 CFR 41.37(c)(1)(ix)).

9. ☒ The brief does not contain copies of the decisions rendered by a court or the Board in the proceeding identified in the Related Appeals and Interferences section of the brief as an appendix thereto (37 CFR 41.37(c)(1)(x)).

10. ☒ Other (including any explanation in support of the above items):

The brief does not comply it has a combination of both rules. Please correct using 37 CFR 41.37 © rule. The III. Status of Claims, V. Summary of Claimed Subject Matter, IX. Evidence Appendix and X. Related Proceedings Appendix are missing, please correct. The statement of facts appears to be the Summary of Claimed Subject Matter section. The VIII. Claims Appendix requires a clean copy .

Bridget C. Monroe
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Patent Appeals Center Specialist
571-272-1651